Diseases of abnormal protein glycosylation: an emerging area.

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Protein glycosylation is a ubiquitous posttranslational modification. Most proteins in the plasma and the extracellular matrix contain covalently bound carbohydrate units as do the majority of proteins in the plasma membrane of cells. Several intracellular proteins, including lysosomal acid hydrolases, are also glycosylated. The number of oligosaccharide units per molecule varies greatly, ranging from only one, as in IgG subunits, to hundreds, as in the mucins. The structures of the oligosaccharide units present on the proteins are also quite diverse, but they fall into two basic types defined by their linkage to the protein backbone. Most commonly, the O-linked oligosaccharides are bound to the hydroxyl group of serine or threonine via an N-acetylgalactosamine residue, whereas the N-linked oligosaccharides are bound to the amide group of asparagine via an N-acetylglucosamine residue. The biosynthetic pathways for the assembly of these two classes of oligosaccharides are quite elaborate, involving numerous glycosyltransferases which sequentially attach sugars one at a time to the growing oligosaccharide unit using either nucleotide-linked sugars or dolichol phosphate–linked sugars as donors for the transfer reactions. In the case of N-linked oligosaccharides, a series of processing glycosidases also trims away sugars to allow the generation of more complex structures (1). The end result is that a vast array of oligosaccharide structures is assembled, some of which are present on only a subset of proteins (such as lysosomal acid hydrolases), whereas others are synthesized in a tissue- or cell type–specific manner. What is the purpose of this complex biosynthetic apparatus? It is now clear that the oligosaccharide units of glycoproteins serve a variety of functions (2). These include participation in the folding of nascent proteins in the endoplasmic reticulum, protection of the underlying protein from the action of proteases, and modulation of the biologic activity of the protein. Oligosaccharides also serve as specific recognition molecules for the intracellular targeting of proteins, the clearance of proteins from the plasma, and the cell–cell interactions that characterize the homing of lymphocytes and other cells of the hematopoietic system.

Considering the prevalence of glycosylation and the multiple functions of the oligosaccharide units, one would expect that genetic defects that impair the biosynthesis of these structures would be detrimental and result in clinical syndromes. Indeed this is the case, and the list of diseases due to abnormal protein glycosylation is growing steadily. The first diseases of this type to be recognized were mucolipidosis II (I-cell disease) and mucolipidosis III (Pseudo-Hurler polydystrophy) where a defect in UDP-GlcNAc:lysosomal enzyme and mucolipidosis III (Pseudo-Hurler polydystrophy) where a defect in UDP-GlcNAc:lysosomal enzyme

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blocks the conversion of fructose 6-phosphate to mannose 6-phosphate, resulting in an inadequate production of dolichol-P-P-oligosaccharide and impaired N-linked glycosylation. Cells lacking PMI can still synthesize mannose 6-phosphate from external mannose and from mannose generated from the breakdown of glycoproteins in lysosomes, but apparently these pathways do not supply sufficient mannose in the patient. This prompted the authors to administer oral mannose to the patient. Within a few weeks, symptoms disappeared and at 11 mo the level of glycosylation of several plasma glycoproteins was shown to be almost normal. While these results must be interpreted with caution since they deal with a single patient treated for a relatively short time, they point to the fact that this genetic disease of protein glycosylation may be treatable in a rational manner based on our understanding of the underlying biochemical pathways.

It is striking that the clinical picture in this patient is fundamentally different from that of the previously described patients with the CDG syndrome although the extent of impaired glycosylation of transferrin, the diagnostic marker, is similar. While the basis for this difference is not understood, it may relate to the fact that phosphomannomutase deficiency impairs mannose utilization for glycoprotein biosynthesis from both glucose and mannose, whereas PMI deficiency only blocks utilization from glucose. Thus it could be that some cell types, such as neurons, are particularly effective in taking up external mannose or reusing mannose generated by the breakdown of glycoproteins. Regardless of the explanation, this patient illustrates that the clinical spectrum of the CDG syndrome is broader than recognized previously. It seems likely that the clinical spectrum will prove to be even greater as clinicians become aware of this disorder and screen their unusual patients for the presence of abnormal protein glycosylation.

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